# InterGenetics' Comments to the Draft Guidance for Industry, Clinical Laboratories, and FDA Staff, In Vitro Multivariate Index Assays Draft Guidance, Issued September 7, 2006

**Introduction:**
We wish to formally respond to the Draft Guidance issued on September 7, 2006 by the FDA for In Vitro Multivariate Index Assays. These comments reflect our belief and explain the effect of such guidance on InterGenetics and our industry. We offer these comments as a helpful consideration in the process of seeking ways to better protect the safety and welfare of the public.

**Our Company:**
InterGenetics Incorporated is a development stage biotechnology organization with research and development in the area of genetic-based screening for breast cancer risk. We are focused on understanding the role that multiple single nucleotide polymorphisms (SNP), along with personal history measures, contribute to a woman's risk for developing breast cancer at various stages in life. This effort began 13 years ago at two research foundations, from which the company was spawned in 1999. We have accumulated over 8,000 specimens, under IRB approval and with appropriate informed consent, from women with and without breast cancer, in 5 geographic regions of the country. From this population, we genotyped 117 different common, but weakly penetrant SNPs believed to be involved in breast carcinogenesis. Our genotype database includes over one million different genotypes in addition to multiple personal history measures of women with and without the disease. This represents one of the largest genotyped case-control studies for breast cancer risk in the country. Our goal has been to identify risk associations through multiple interactions of gene-gene and gene-personal history measures that could lead to a better understanding of the likelihood of a particular woman developing a diagnosis of breast cancer. With such a tool, clinicians can then focus their attention on the high-risk patients and to employ more comprehensive screening tools along with potential use of preventive medicines and lifestyle changes. This effort would lead to more effective breast cancer risk research and the definition of best practices that may in turn lead to earlier detection, reduction of risk and breast cancer prevention.

**Interaction with the FDA:**
In 2002, during the early stages of the company development, we initiated communications with the FDA regarding our test and the route for development as a CLIA based testing service with the reporting of results from an algorithm. We sought guidance from the FDA as we were preparing to raise a significant amount of capital over the next several years, all from individual investors. We received guidance and confirmation from senior officials in the In Vitro Diagnostic Device (IVD) branch of the FDA[1] that the development path we were following was correct and not in violation of FDA regulations, and that premarket approval was not necessary for our clinical laboratory testing service provided it was only run in our single laboratory in Oklahoma City.

Previously, individuals at InterGenetics had worked with the IVD office on four approved premarket filings and a CLIA waiver, and found Dr. Gutman and his staff to be most helpful, candid and efficient in all dealings with them. Because of the helpful counsel and guidance previously received from them, we felt confident that by accomplishing the understood objectives and managing the changing nature of scientific discovery, InterGenetics had a defined course that would ultimately lead to a marketed product.

[1] Telephone and written communications with Dr. Steven Gutman and Dr. Joseph Hackett during the period of June 26, 2002 to July 10, 2002

**InterGenetics Situation:**
After confirming our direction as a CLIA based laboratory service with the FDA as an appropriate route, and relying on the Agency's guidance, we continued our R&D and pursued the development path towards building a CLIA laboratory with a service-based test for breast cancer risk assessment. We continued down this path for four additional years, developing our genotyping methods, increasing our specimen collection and raising three rounds of financing totaling $12.5MM with grants of about $2.5MM to complete our research & development work. We initiated and funded several collaborations with well known academic cancer institutions in order to further the research, publish the findings and establish partnerships to further this research.

We built and equipped a CLIA based laboratory[2] with the necessary infrastructure. We established a sophisticated Laboratory Information Management System (LIMS) and then hired the appropriate CLIA required medical, clinical and technical staffing. We simultaneously spent approximately two years recruiting testing centers nationwide as well as prequalifying them, as it was our requirement that they be operated by either breast surgeons or radiologists specializing in mammography and breast care. We also required that testing centers have genetic counseling capabilities and methods to manage the high-risk patient along with more comprehensive surveillance modalities before we allowed them to be included into the Breast Cancer Risk Testing Network. In order to help patients better understand genetics and breast cancer risk, we funded a significant 12 month project with i.d.e.a.s., the former storytelling arm of the MGM/Disney studio, to create a novel patient education and physician education interactive tool that was put together with the help of physicians and genetic counselors with experience operating a high-risk clinic for breast cancer.

In January 2006, about one month before our planned product launch in centers across the country, we received a telephone call from the FDA Compliance Office indicating that they wanted to visit with us, and that we may not be in compliance with FDA regulations. We indicated that we were appropriately compliant with CLIA regulations and had previously received and relied upon guidance from the FDA, but would be glad to meet with the FDA and present our research and compliance program regarding our CLIA laboratory test service. Shortly after that we received a formal letter inviting InterGenetics to have a meeting with the FDA to discuss our test and that the FDA considered OncoVue® a "device" under the Federal Food, Drug, and Cosmetic Act. [3] We immediately scheduled a meeting with the IVD branch of the FDA anticipating that this could all be cleared up by demonstrating our compliance with CLIA, outlining our research and clinical development work, along with our following the FDA guidance received in 2002. During our meeting on February 21, 2006, to our complete surprise and shock, we were told that the laboratory portion of our test was appropriately CLIA regulated, but that the computer rules or algorithm made us regulated as a device. As such, we were further informed that we would need to go through a premarket approval process before bringing our clinical laboratory testing service to market and that we could not market our test until approved. This was unfathomable because we were aware of no other CLIA laboratory based company required to meet this regulatory requirement the FDA was imposing, but rather similar companies with similar genetic platforms and algorithms were currently in the market and had been for multiple years,. The inequity and the consequences to InterGenetics were severe.

The FDA meeting occurred two weeks before our scheduled product launch and this created a dire situation. Additional funding was expected from investors once we launched our product, not to mention anticipated product revenue to offset the need for additional funding. This necessitated informing all our shareholders and potential investors that we were now required to seek FDA approval prior to commercialization. The backlash was significant. Some investors disappeared. Some investors who had invested but had outstanding commitments were upset that we originally told them we did not need FDA approval, and they said, "…had they known this,

[2] CLIA ID number 37D1047365, Effective November 2, 2005
[3] See attached letter dated January 27, 2006

they probably would not have invested!" We were astonished with the FDA's position, that without precedent, no notice, no guidance and no time to formally comment, we were thrown into an unclear direction regarding FDA compliance.

Our situation is ongoing and has not improved. There still is tremendous inequity between InterGenetics' regulatory requirements and those of others in the same industry, including those now defined by the new IVDMIA guidance. InterGenetics' fate has been dramatically altered by the seemingly arbitrary and inequitable treatment by the FDA. Our financial situation has not improved and is a direct result of the uncharacteristic actions taken by the FDA on selective portions of an industry. We are hung in regulatory limbo and are in need of some immediate action by the FDA. However, in spite of this ordeal, over the past seven months we have taken a proactive approach to work with the FDA in this situation. We immediately submitted the appropriate data, clinical study protocols and application for an Exploratory Investigational Device Exemption, and we recently received a conditional IDE approval[4].

**InterGenetics Position on FDA regulation of IVDMIA**

It is our understanding that current regulations provide for regulatory oversight through CMS and FTC of laboratory based testing. We understand that improvements in technology may often warrant additional regulations to keep up with changes in technology. We also believe that ultimately genetic tests, and other analytes of sophistication, could greatly benefit from improvements in regulation. Improved or clarified regulation can help make clear the distinction between unscrupulous, illegitimate "genetic" testing companies that prey on unknowledgeable consumers, and the legitimate companies that have painstakingly gone through the scientific rigor of R&D and scientific validation, and worked to provide helpful tools to the medical community. We do not have issues with improvements in regulation but rather, we have **STRONG** opposition with the **IMPLEMENTATION** process being enforced and the path chosen because of the following:

1. Clinical laboratory testing including those such as OncoVue® have been heretofore regulated effectively through CMS under the Clinical Laboratory Improvement Amendment of 1988.

2. Few, if any, individuals in the industry knew of these immediate regulatory rule changes, implementation and enforcement, and few, if any, understood what constituted the laboratory testing services that would be regulated.

3. Prior to September 7, 2006, (over seven months after InterGenetics received a noncompliance letter from the FDA regarding our testing service), no guidance was available such that one could know what the FDA's intent was as it applied to "home-brew" laboratory based genetic tests operating in a single laboratory.

4. This immediate enforcement agenda gave no time to respond, plan, anticipate or make adjustments on industry's part, particularly for those with long term, capital intensive timelines and either products positioned to be marketed or products already on the market.

5. It appears questionable as to whether or not the FDA's actions have been consistent with the notice-and-comment rulemaking requirements under applicable laws. Communications to selected companies seemed to be stealthily conducted and on an individual basis, picking out companies and requesting they come in for review. This is in direct opposition to the FDA good guidance policy which states in 21 CFR section 10.115:

*(e) Can FDA use means other than a guidance document to communicate*

[4] InterGenetics IDE G060046 conditional approval dated September 8, 2006

*new agency policy or a new regulatory approach to a broad public audience? The agency may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time. These GGP's must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public* audience.

6. No guidance currently exists on how to comply with the FDA premarket requirements of QSR, GMP and Design Control as it relates to laboratory services rather than devices, and it is not clear how these will be resolved because it involves regulation by both CMS and the FDA and regulatory conflicts are sure to be inherent.

7. It appears that not much though has gone into the consequences of these sweeping regulatory changes, nor the issues and challenges that would be created for organizations required to meet BOTH CLIA and FDA premarket approval regulations. It is also not clear which regulatory agency would be responsible for overlapping or conflicting issues.

8. The IVD Office of the FDA does not have appropriations or staff to handle the workload anticipated by this immediate change in regulatory position. Medical Device Users fee revenue for staff hires cannot be expected since most of these companies would fall into a first-time exclusion.

9. With no guidance on how to deal with the above mentioned issues, the most likely scenario is that all these tests would be backlogged in the FDA potentially for years.

The enormity and magnitude of problems created by this heavy-handed immediate enforcement approach does not bode well for the FDA, CMS the industry and ultimately, the practitioner and patient. There are approximately 900 genetic-based tests operating as “home-brew” tests. If we assume that conservatively 30% of them fall into the new category of IVDMIA, then all at once 270 premarket reviews will be required to be submitted and approved prior to these tests being legally used in the clinic. This does not account for the hundreds of other “home-brews” based upon proteins, cytokines and other markers. All total there could be more than 500 currently used IVDMIA’s immediately required to receive a premarket approval from the FDA prior to legally being on the market if this immediate enforcement position is upheld.

**InterGenetics Recommendation to the FDA**

We believe that the existing regulatory framework enables sufficient oversight under existing laws and can be managed by augmenting the CLIA regulations to address any specific safety concerns of the FDA. However, if the FDA has already chosen to take the course of action for regulation of IVDMIA’s, we strongly recommend that **at the very least** a transition approach be taken with the following recommendations:

1. First, develop and issue all guidance necessary for compliance with the intents of the FDA and allow the public and industry to respond within an appropriate timeframe.

2. Further define the subcategory of IVDMIA, what tests are included and what tests are not. An algorithm can be as simple as computer rules or as complicated as software code to output results. Does this make all multianalyte tests that use some form of IT an algorithm?

3. Clearly define regulatory responsibilities along FDA and CMS lines outlining who does what and how the interaction and interface will be handled.

4. Create an ombudsman for problems that do not get an agency to be responsive.

5. Provide guidance on how companies can be expected to meet the Device Design, GMP and QSR as it relates to laboratory services or alternatively, what substitutes satisfy the FDA's device requirements for these tests.

6. Request Congress to appropriate funds to the FDA and CMS for managing and approving the large backlog of IVDMIA applications that will be submitted to comply with the new guidance.

7. Provide a transition period and a future date certain that all companies falling into the IVDMIA must be compliant. This provides equity for companies who have built businesses according to the past guidance to ensure that developing companies would not be inequitably treated compared to those with tests now on the market.

8. Allow all companies, including those with existing products in the market, time to transition and prepare a premarket application and allow adequate time for a decision to be rendered.

This document is addressing a clinical laboratory service prescribed or utilized by trained medical staff in a clinical setting, with test results being reported to a clinician who interprets and advises their patient. We are not addressing testing that bypasses the clinician and markets direct-to-consumer where test prescribing and results completely bypasses a trained and credentialed medical professional.

If the pressure leading to immediate enforcement and regulation change is motivated by the proliferation of a few unscrupulous companies preying on the unsuspecting public with bogus claims and unsubstantiated labeling, we recommend enforcement action on those companies through existing enforcement laws. If existing laws don't differentiate enough to separate the credible from the incredible, enact enforcement laws that deal with those issues rather than making all the ethical, and academically rigorous and scientifically sound businesses suffer for the sins of a few. If the problem lies with the exceptions in the industry then deal with them directly and don't destroy a system that has worked for decades only to reign in a few. Instead, improve the existing CMS CLIA system over time so that it does not irreparably damage individual companies, damage the IVD FDA's reputation and credibility and, in the meantime, bring chaos to the industry and medical community currently using these critical tests.

We understand and appreciate the need to ensure the safety and welfare of the public for genetic testing and other multivariate index assays. This is precisely why InterGenetics selected only medical centers to offer our test, with clinicians who had experience to care for high risk patients and had comprehensive surveillance methods for early detection of breast cancer. We know that almost 90% of women who contract breast cancer do not have a first-degree relative with the disease[5], so the vast majority of breast cancer risk in individuals is not effectively identified. The counterpoint to these regulatory changes is that these burdensome approaches and changes which have no precedent in the clinical laboratory will delay, impede or even prevent medical progress in the early detection, treatment and prevention of breast cancer. Such changes, as those being implemented by the FDA will prevent other medical institutions from establishing R&D entities like InterGenetics, because of the regulatory uncertainty and financial challenges that accompany these burdensome regulations.

[5] American Cancer Society